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## Smoking and Cancer

# Impact of changing US cigarette smoking patterns on incident cancer: risks of 20 smoking-related cancers among the women and men of the NIH-AARP cohort

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## Abstract

**Background:** Historically, US women started smoking at a later age than men and had lower relative risks for smoking-related cancers. However, more recent birth cohorts of women and men have similar smoking histories and have now reached the high-risk age for cancer. The impact of these changes on cancer incidence has not been systematically examined.

**Methods:** Relative risks (RR), 95% confidence intervals (CI) and attributable fractions were calculated for cigarette smoking and incidence of 20 smoking-related cancers in 186 057 women and 266 074 men of the National Institutes of Health-AARP cohort, aged 50 to 71 years in 1995 and followed for 11 years.

**Results:** In the cohort, which included participants born between 1924 and 1945, most women and men started smoking as teenagers. RRs for current vs never smoking were similar in women and men for the following cancers: lung squamous-cell (RR women: 121.4, 95% CI: 57.3–257.4; RR men: 114.6, 95% CI: 61.2–214.4), lung adenocarcinoma (RR women: 11.7, 95% CI: 9.8–14.0; RR men: 15.6, 95% CI: 12.5–19.6), laryngeal (RR women: 37.0, 95% CI: 14.9–92.3; RR men: 13.8, 95% CI: 9.3–20.2), oral cavity-pharyngeal (RR women: 4.4, 95% CI: 3.3–6.0; RR men: 3.8, 95% CI: 3.0–4.7), oesophageal squamous cell (RR women: 7.3, 95% CI: 3.5–15.5; RR men: 6.2, 95% CI: 2.8–13.7), bladder (RR women: 4.7, 95% CI: 3.7–5.8; RR men: 4.0, 95% CI: 3.5–4.5), colon (RR women: 1.3, 95% CI: 1.2–1.5; RR men: 1.3, 95% CI: 1.1–1.4), and at other sites, with similar attributable fractions.

**Conclusions:** RRs for current smoking and incidence of many smoking-related cancers are now similar in US women and men, likely reflecting converging smoking patterns.

**Key words:** Cigarette smoking, cohort, cancer, men and women

#### Key Messages

- In the late 19th and early 20th centuries, US women typically started smoking cigarettes later in life than men and tended to have lower relative risks for cigarette smoking and different types of incident cancer.
- By the 1960s, age at initiation in women had decreased to that of men. The NIH-AARP cohort is one of the first to include these birth cohorts of women, allowing direct comparisons of disease risks in men and women with largely similar lifetime exposures.
- In the NIH-AARP cohort that included women and men with similar lifetime smoking histories, women and men had similar relative risks for cigarette smoking and many types of incident smoking-related cancer.

## Introduction

The 1964, the US Surgeon General's Report concluded that cigarette smoking causes lung cancer in men.<sup>1</sup> Later studies extended these findings to women and to numerous other cancer sites.<sup>2,3</sup> However, dramatic subsequent changes in smoking patterns<sup>2</sup> may have affected the magnitude of smoking-related cancer risks.

In the 1920s, most US cigarette smokers were men who had started smoking in their teenage years.<sup>4,5</sup> In contrast, cigarette smoking did not become common among women until World War II. Furthermore, age at initiation tended to be later in women than in men until the 1960s.<sup>4–6</sup> These birth cohorts have only recently reached the high-risk age for cancer. Previous epidemiological studies largely included women who started smoking later in life, and therefore may underestimate the contemporary risks of currently smoking women.<sup>6</sup> Indeed, recent data for overall mortality and the most common causes of death, including mortality from lung cancer, indicate that the RRs for current vs never smoking increased in US women over the course of the 20th century to reach that of men.<sup>7</sup> However, few comparable data for the incidence of different cancer types by sex are available.

Other historical changes may also have affected cancer risks, including widespread use of filters, blended tobacco and other changes to cigarettes.<sup>2,8,9</sup> Such changes are thought to have contributed to changes in the histological distribution of lung cancer and also may have affected disease risks. Contemporary smokers in the USA also tend to have lower socioeconomic status than smokers of the past.<sup>10</sup>

We examined associations between cigarette smoking and incidence of 20 smoking-related cancers<sup>3</sup> in the

women and men of the NIH-AARP study,<sup>11</sup> a large contemporary cohort in which most women and men began smoking in their teenage years. To examine possible changes in RRs over time, we systematically reviewed US studies of smoking and histological subtype of lung cancer (adenocarcinoma, small-cell, squamous-cell and undifferentiated) and anatomical subtype of head and neck cancer (larynx, oral cavity, and pharynx), sites with strong associations and substantial previous literature.

## Methods

### Study population

The NIH-AARP (National Institutes of Health-AARP) Diet and Health Study<sup>11</sup> was initiated in 1995–96 when a questionnaire was mailed to 3.5 million AARP members between the ages of 50 and 71, who lived in: California; Florida; Louisiana; New Jersey; North Carolina; Pennsylvania; Atlanta, Georgia; or Detroit, Michigan. Questionnaires were returned by 617 119 participants, 566 398 of whom completed them in satisfactory detail.

The NIH-AARP was approved by the Special Studies Institutional Review Board of the NCI and participants gave informed consent by virtue of completing and returning the questionnaire.

We excluded proxy respondents ( $n = 15\,760$ ), those with prevalent (except non-melanoma skin cancer) cancer at baseline ( $n = 51\,234$ ), those lacking information on tobacco smoking ( $n = 31\,867$ ), those who did not smoke cigarettes but smoked pipes or cigars ( $n = 15\,367$ ) and those

who died before their completed questionnaire was scanned, which was set as the first day of follow-up ( $n = 40$ ). Our analytical cohort included 186 057 women and 266 074 men.

### Cohort follow-up

Cohort members were followed by annual updates to the US Postal Service National Change of Address database and participant change of address requests. Vital status was assessed via the Social Security Administration Death Master File and National Death Index.

'Smoking-related cancers', as defined by the International Agency for Research on Cancer (IARC),<sup>3</sup> were identified by the cancer registries of 11 states (eight baseline states plus Arizona, Nevada and Texas).<sup>12</sup> Site of first primary incident cancer was defined using the International Classification of Disease for Oncology site<sup>13</sup> and oesophagus, lung and ovary histology codes. We also combined cancers of the oral cavity and pharynx together to facilitate comparisons with previous studies.

Follow-up time ended at incident cancer diagnosis, death, movement out of the catchment area or 31 December 2006, whichever came first.

### Exposure assessment

We assessed tobacco smoking, demographics and other exposures via baseline questionnaire. Ever smokers were participants who reported smoking 100 cigarettes during their lifetime. We assessed the typical number of cigarettes smoked per day, current or former smoking status and years since cessation for former smokers. Participants reporting quitting in the previous year were considered to be current smokers. To calculate duration of smoking, we used data on age at initiation that were available for a majority of the cohort ( $n = 290\,242$ ;  $n = 152\,644$  ever smokers) who answered a later questionnaire in 2004–06. For those lacking age at initiation, we imputed 17 years as this was the mid point of both female and male participants' most common response category (15 to 19 years) and corresponds with national surveys. Pack-years of smoking were determined by multiplying cigarettes per day by smoking duration.

### Statistical methods

Analyses were conducted using SAS version 9.1. Statistical tests were two-sided. Age-standardized incidence rates per 100 000 person-years and 95% confidence intervals (CI) were calculated for men and women separately, using

5-year age bands standardized to the entire NIH-AARP study population.

Sex-stratified RRs and 95% CIs were obtained from Cox proportional hazards regression models, with adjustment for age, education, alcohol, self-reported ethnicity and smoking pipes or cigars. We provide relative risks for categories of smoking with three or more cases. Inclusion of additional lifestyle and dietary variables, including: consumption of fruits, vegetables and red meat; body mass index; physical activity; and menstrual and reproductive factors (women), had only minor effects on relative risks and were excluded to facilitate comparisons with earlier studies.

Population attributable fractions (AFs) for ever smoking were calculated from multivariate-adjusted beta-coefficients with 95% CIs.

### Systematic review of previous studies

Due to strong associations between smoking and each major histological subtype of lung cancer, as well as anatomical sites of head and neck cancer, we systematically reviewed previous US studies of these associations to identify temporal changes in relative risk. Details of our search and selection criteria are provided in the Supplement (available as [Supplementary data](#) at *IJE* online). We identified 21 lung cancer studies providing relative risks by histological subtype and 24 studies of head and neck cancer that provided relative risks by anatomical sub-site. These studies were conducted between 1949 and 2009.

### Results

At baseline, 17% of women and 13% of men were current smokers, and 44% of women and 26% of men were never smokers ([Supplementary Table 1](#), available as [Supplementary data](#) at *IJE* online). Current smokers tended to have less education than never smokers. Among participants with data on age of initiation, the most common category of initiation was age 15–19 (43% of female and 41% of male current smokers), although more men (33%) started smoking before age 15 than women (16%). Few men (2%) or women (6%) started smoking after age 25.

Incidence rates among current smokers were higher than among never smokers for all 20 examined cancer sites ([Supplementary Tables 2–3](#), available as [Supplementary data](#) at *IJE* online) in both women and men. Among female current smokers, the highest incidence rates were observed for lung cancer, followed by colon, bladder, pancreas, and oral cavity and pharynx. Among male current smokers, the most common cancers, in order, were lung, bladder, colon, oral cavity and pharynx, and kidney. In general, incidence

rates tended to be higher in men than women, among both current smokers and among never smokers.

RRs for current vs never smoking nearly always reached statistical significance, even for hypopharynx, renal pelvis and other sites with relatively low incidence (Figure 1; Supplementary Tables 2–3). The strongest associations were observed for cancers of the respiratory tract, including larynx and lung; RRs for oesophageal squamous-cell, oral cavity and urinary tract cancers also reached 4 or higher.

RRs for current smoking in women were largely comparable to that for men, with overlapping CIs (Figure 1; Supplementary Tables 2–3). AFs for ever smoking were also similar (Figure 1). We observed this pattern for major lung cancer subtypes: squamous-cell (women, RR: 121.4, 95% CI: 57.3–257.4, AF for ever smoking: 97%; men, RR: 114.6, 95% CI: 61.2–214.4, AF: 97%), small-cell (women, RR: 73.1, 95% CI: 43.6–122.8, AF: 94%; men, RR: 73.1, 95% CI: 41.1–130.2, AF: 94%), undifferentiated (women, RR: 32.0, 95% CI: 15.4–66.2, AF: 89%; men, RR: 39.5, 95% CI: 19.2–81.2, AF: 90%), adenocarcinoma (women, RR: 11.7, 95% CI: 9.8–14.0, AF: 74%; men, RR: 15.6, 95% CI: 12.5–19.6, AF: 82%) and other sites as well, although confidence intervals for less common sites were sometimes wide.

For example, similar RRs and AFs were observed in women and men for oesophageal squamous-cell (women, RR: 7.3, 95% CI: 3.5–15.5, AF: 56%; men, RR: 6.2, 95% CI: 2.8–13.7, AF: 63%), oesophageal adenocarcinoma (women, RR: 2.4, 95% CI: 1.0–5.9, AF: 37%; men, RR: 2.9, 95% CI: 2.1–4.1, AF: 44%), cancers of the bladder (women, RR: 4.7, 95% CI: 3.7–5.8, AF: 52%; men, RR: 4.0, 95% CI: 3.5–4.5, AF: 52%), renal pelvis (women, RR: 7.0, 95% CI: 3.2–15.4, AF: 50%; men, RR: 4.2, 95% CI: 2.1–8.4, AF: 57%), oral cavity and pharynx (women, RR: 4.4, 95% CI: 3.3–6.0, AF: 46%; men, RR: 3.8, 95% CI: 3.0–4.7, AF: 36%), pancreas (women, RR: 2.3, 95% CI: 1.8–2.8, AF: 18%; men, RR: 2.0, 95% CI: 1.6–2.4, AF: 13%) and colon (women: RR: 1.3, 95% CI: 1.2–1.5, AF: 9%; men, RR: 1.3, 95% CI: 1.1–1.4, AF: 11%). Although RRs were higher in men for some sites, such as liver (men, RR: 2.7, 95% CI: 1.9–3.8, AF: 31%; women, RR: 1.6, 95% CI: 0.9–2.6, AF: 19%), RRs for others, such as larynx, were higher in women (women, RR: 37.0, 95% CI: 14.9–92.3, AF: 88%; men, RR: 13.8, 95% CI: 9.3–20.2, AF: 74%).

We observed a dose-response for nearly all examined sites, with higher incidence rates and RRs observed with smoking more cigarettes per day. RRs for cigarettes per day (Tables 1 and 2) and pack-years (Supplementary Tables 4–5, available as Supplementary data at *IJE* online) were generally similar between women and men for each cancer site.

Similar patterns for current vs never smoking and each incident cancer were also observed among each stratum of educational status (Supplementary Tables 6–7, available as Supplementary data at *IJE* online), although our confidence intervals were often wide.

To evaluate possible historical changes, we compared our results for lung, laryngeal, oral cavity and pharyngeal cancers with previously published US studies by systematic review (plotted chronologically in Figures 2 and 3 and listed in Supplementary Tables 8–12, available as Supplementary data at *IJE* online). As most previous studies combined cancers of the oral cavity and pharynx together, we did the same. In studies conducted before 1970, that included participants born in the late 19th and early 20th centuries, RRs for current vs never smoking were lower in women than in men (RRs for lung adenocarcinoma: 0.6–1.5 in women vs 1.5–4.6 in men; RRs for lung squamous-cell cancer: 2.6 and 3.0 in women vs 8.3 and 22.9 in men; RRs for laryngeal cancer: 3.8 in women vs 5.8–23.4 in men; RRs for oral cavity and pharyngeal cancer: 2.0 and 2.6 in women vs 3.1–6.3 in men).

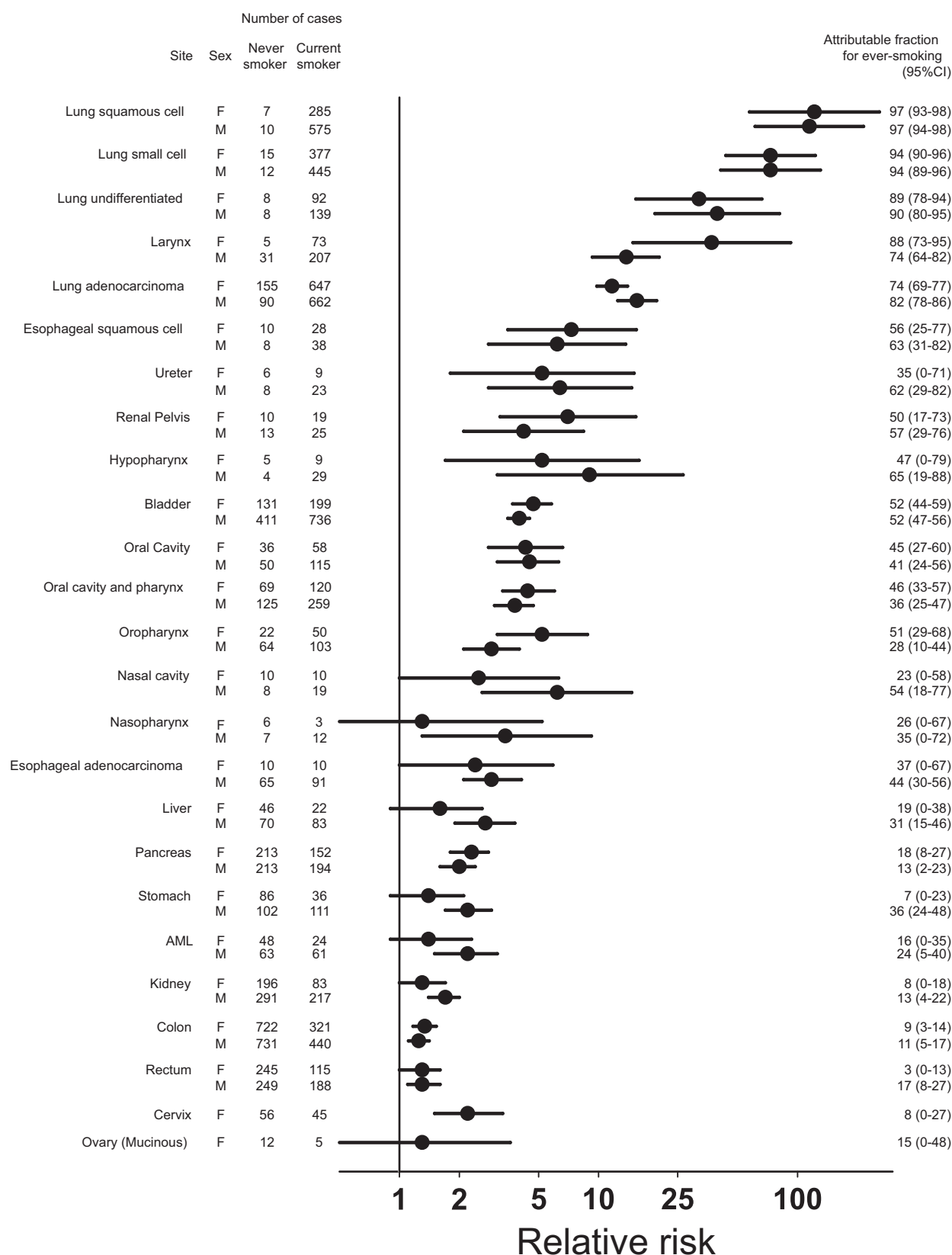
For women (Figure 2), RRs increased over time for each of these cancer types (comparing RRs in studies conducted prior to 1970 with the current study: lung adenocarcinoma: 0.6–1.5 vs 11.7; lung squamous-cell cancer: 2.6 and 3.0 vs 121.4; laryngeal cancer: 3.8 vs 37.0; and oral cavity and pharyngeal cancer: 2.0 and 2.6 vs 4.4) and became similar to RRs in men. Similar patterns were also seen for small-cell lung cancer, although we identified fewer previous studies (Supplementary Table 8).

In contrast to trends among women, RRs for current vs never smoking with laryngeal and oral cavity and pharyngeal cancer in men did not appear to change over time (Figure 3). However, RRs for lung adenocarcinoma (for example, 15.6 in the current study) and lung squamous-cell cancer (114.6 in the current study) were higher in the more recent studies than in earlier studies, as we had observed for women. Similar patterns were again observed for small-cell lung cancer.

In both women and men, increasing RRs for cigarette smoking and lung cancer persisted among categories of cigarettes per day and pack-years of smoking (Supplementary Tables 9 and 10).

## Discussion

Relative risks for current smoking and each smoking-related cancer were broadly similar in the women and men of the NIH-AARP cohort, with largely overlapping confidence intervals. In contrast, data from our systematic review indicate substantially lower RRs in women relative to men in US studies conducted before 1970, which included



**Figure 1.** Associations of current vs never cigarette smoking with 20 smoking-related cancer sites in women and men. Relative risks on the log scale are on the x-axis, with each cancer site listed on the y-axis. Plotted circles represent the point estimate and whiskers reflect the 95% confidence intervals. Horizontal line represents a relative risk of 1. Relative risks are adjusted for age, education, alcohol intake, self-reported ethnicity and smoking pipes or cigars. Never smokers are participants who did not smoke cigarettes, pipes or cigars. Attributable fractions and associated 95% confidence intervals for ever smoking are also included.



**Table 1.** Cigarettes per day among current smokers and cancer in women

Smoking use	Never <sup>a</sup> 1–10 cigarettes per day			11–20 cigarettes per day		20–40 cigarettes per day		> 40 cigarettes per day	
Number in cohort	82 032 9784			13 513		8017		630	
Cancer type	Case (n)	Case (n)	Relative risk <sup>b</sup> (95% CI)	Case (n)	Relative risk <sup>b</sup> (95% CI)	Case (n)	Relative risk <sup>b</sup> (95% CI)	Case (n)	Relative risk <sup>b</sup> (95% CI)
<b>Oral cavity and pharynx</b>	69	23	2.9 (1.8–4.8)	56	5.2 (3.6–7.4)	37	5.8 (3.8–8.8)	4	8.0 (2.9–22.2)
Oral cavity	36	8	2.2 (1–4.7)	30	5.6 (3.4–9.2)	20	6.5 (3.7–11.4)	0	nd
Oropharynx	22	11	3.8 (1.8–7.9)	21	5.3 (2.8–9.7)	15	6.1 (3.1–12.2)	3	15.2 (4.4–52)
Hypopharynx	5	1	nd	5	7.6 (2.1–27.1)	2	nd	1	nd
Nasopharynx	6	3	4.3 (1–17.9)	0	nd	0	nd	0	nd
<b>Respiratory tract</b>									
Nasal cavity	10	1	nd	3	1.6 (0.4–5.9)	6	5.5 (1.9–16)	0	nd
Larynx	5	11	18.4 (6.3–53.3)	29	37.1 (14.3–96.6)	29	65.2 (24.9–170.9)	4	118.8 (31.4–449.4)
Lung	281	375	12.2 (10.4–14.2)	800	19.8 (17.3–22.7)	643	28.4 (24.6–32.8)	75	44.2 (34.2–57.2)
Lung adenocarcinoma	155	131	7.4 (5.9–9.4)	287	12.4 (10.2–15.2)	204	15.7 (12.7–19.5)	25	25.7 (16.8–39.4)
Lung small-cell	15	62	38.4 (21.8–67.6)	148	70.2 (41.2–119.7)	151	129.3 (75.7–220.7)	16	185.8 (91.4–377.7)
Lung squamous-cell	7	57	74 (33.7–162.6)	126	127.6 (59.5–273.9)	93	173.8 (80.3–376.3)	9	233.7 (86.6–630.6)
Lung undifferentiated	8	24	26.2 (11.7–58.6)	44	37 (17.3–79.2)	23	34.1 (15–77.4)	1	nd
<b>Alimentary tract</b>									
Oesophageal squamous-cell	10	3	2.1 (0.6–8)	20	12.6 (5.7–28.1)	5	5.4 (1.8–16.7)	0	nd
Oesophageal adenocarcinoma	10	1	nd	3	1.6 (0.4–6.2)	6	5.4 (1.8–16.2)	0	nd
Stomach	86	10	1.1 (0.6–2.2)	17	1.6 (0.9–2.6)	7	1.2 (0.5–2.6)	2	nd
Colon	722	101	1.3 (1.1–1.6)	146	1.5 (1.2–1.8)	73	1.4 (1.1–1.7)	1	nd
Rectum	245	30	1.1 (0.7–1.6)	55	1.5 (1.1–2)	24	1.2 (0.8–1.8)	6	4.0 (1.7–9)
Liver	46	6	1.3 (0.5–3)	11	1.7 (0.9–3.4)	4	1.1 (0.4–3.2)	1	nd
Pancreas	213	58	2.6 (2.0–3.5)	60	2.1 (1.6–2.8)	32	2.0 (1.4–2.9)	2	nd
<b>Urinary tract</b>									
Bladder	131	50	3.5 (2.5–4.9)	82	4.5 (3.4–5.9)	63	6.2 (4.5–8.4)	4	5.2 (1.9–14.1)
Renal pelvis	10	3	3.4 (0.9–12.4)	9	7.6 (3–19.3)	7	10.7 (3.9–29.4)	0	nd
Ureter	6	2	nd	5	6.3 (1.8–21.7)	2	4.3 (0.8–22.7)	0	nd
Kidney	196	25	1.1 (0.8–1.8)	36	1.3 (0.9–1.8)	18	1.2 (0.7–1.9)	4	3.5 (1.3–9.4)
<b>Other</b>									
AML	48	12	2.4 (1.2–4.5)	8	1.1 (0.5–2.4)	4	1.0 (0.3–2.7)	0	nd
Cervical	56	14	2.1 (1.2–3.8)	16	1.9 (1.1–3.3)	15	3.2 (1.8–5.7)	0	nd
Ovary (mucinous)	12	2	nd	3	1.6 (0.4–5.8)	0	nd	0	nd

nd, not determined; AML, acute myeloid leukemia.

<sup>a</sup>Referent group: never smokers are participants who did not smoke cigarettes, pipes or cigars.<sup>b</sup>Adjusted for age, education, alcohol intake, self-reported ethnicity and smoking pipes or cigars.

participants born in the late 19th and early 20th centuries, for each major histological subtype of lung cancer, as well as for cancers of the larynx and oral cavity and pharynx. Before 1970, women at the ages of highest cancer risk tended to start smoking later in life than men, and thus had less cumulative exposure to cigarettes.<sup>4,5</sup> Typical age at initiation only reached that of men in the 1960s.<sup>4–6,14</sup> The NIH-AARP cohort is one of the first to include these more recent birth cohorts of women, allowing direct comparisons of disease risks in men and women with largely similar lifetime exposures. Our results indicate that the relative risks and population-attributable fractions for cigarette smoking and individual smoking-related cancers are now also similar for

men and women. Although systematic investigations of cigarette smoking and incident cancers among these birth cohorts are not yet available from other US studies, we expect our results to be confirmed as they parallel recent findings for cigarette smoking with total and cause-specific mortality, which were consistent in our cohort and four others.<sup>7,15</sup> Together, these results indicate that with converging patterns of cigarette use, US female and male smokers now have similar cigarette-related RRs for disease.

Unlike women, men have been initiating smoking as teenagers for a century.<sup>4,5</sup> Perhaps reflecting this pattern, the RRs among men for laryngeal, oral cavity and pharyngeal cancer were stable over the years in our systematic



**Table 2.** Cigarettes per day among current smokers and cancer in men

Smoking use	Never <sup>a</sup>			1–10 cigarettes per day		11–20 cigarettes per day		21–40 cigarettes per day		> 40 cigarettes per day	
Number in cohort	68 748 7184			13 314		13 421		13 421		1982	
Cancer type	Case (n)	Case (n)	Relative risk <sup>b</sup> (95% CI)	Case (n)	Relative risk <sup>b</sup> (95% CI)	Case (n)	Relative risk <sup>b</sup> (95% CI)	Case (n)	Relative risk <sup>b</sup> (95% CI)	Case (n)	Relative risk <sup>b</sup> (95% CI)
<b>Oral cavity and pharynx</b>	125	32	2.4 (1.6–3.6)	89	3.6 (2.7–4.8)	117	4.5 (3.4–6.0)	21	5.4 (3.3–8.7)		
Oral cavity	50	12	2.5 (1.3–4.8)	45	5.0 (3.2–7.7)	51	5.5 (3.6–8.4)	7	5.0 (2.2–11.2)		
Oropharynx	64	18	2.7 (1.5–4.6)	31	2.4 (1.5–3.8)	44	3.2 (2.1–4.9)	10	4.9 (2.4–9.8)		
Hypopharynx	4	1	nd	8	7.8 (2.2–27.3)	17	15.2 (4.7–48.4)	3	17.4 (3.6–83.2)		
Nasopharynx	7	1	nd	5	2.8 (0.8–10.1)	5	3.2 (0.9–11.6)	1	nd		
<b>Respiratory tract</b>											
Nasal cavity	8	2	nd	9	7.6 (2.7–21.3)	7	5.9 (2.0–17.7)	1	nd		
Larynx	31	28	9.4 (5.5–15.8)	72	13.1 (8.5–20.3)	87	16 (10.4–24.6)	20	26.2 (14.6–46.8)		
Lung	175	299	17.3 (14.3–20.9)	851	27.9 (23.7–33)	1076	37.7 (32–44.4)	209	53.0 (43.2–65.2)		
Lung adenocarcinoma	90	99	11.5 (8.5–15.4)	248	16.2 (12.6–20.8)	274	19.1 (14.9–24.5)	41	20.9 (14.3–30.6)		
Lung small-cell	12	51	40.8 (21.6–77.1)	153	67.9 (37.5–123)	203	93.6 (51.9–168.9)	38	125.5 (65.0–242.3)		
Lung squamous-cell	10	68	64.5 (33.0–126.0)	185	102.0 (53.7–193.7)	270	160.6 (84.9–303.7)	52	222.5 (112.3–440.9)		
Lung undifferentiated	8	18	24.7 (10.6–57.9)	37	28.7 (13.1–62.6)	73	61.7 (29.1–130.6)	11	67.5 (26.6–171.0)		
<b>Alimentary tract</b>											
Oesophageal squamous-cell	8	4	3.2 (0.9–11)	12	6.0 (2.3–15.4)	19	9.7 (3.9–23.7)	3	9.8 (2.5–39.3)		
Oesophageal adenocarcinoma	65	10	1.6 (0.8–3.3)	37	3.2 (2.1–5)	39	3.5 (2.2–5.4)	5	3.2 (1.3–8.1)		
Stomach	102	27	2.5 (1.6–3.9)	38	2.1 (1.4–3.1)	43	2.5 (1.7–3.7)	3	1.3 (0.4–4.0)		
Colon	731	93	1.3 (1.1–1.7)	161	1.3 (1.1–1.5)	161	1.3 (1.1–1.6)	25	1.4 (0.9–2.1)		
Rectum	249	35	1.1 (0.8–1.7)	75	1.4 (1.0–1.8)	64	1.2 (0.9–1.6)	14	1.7 (1.0–3.0)		
Liver	70	20	2.8 (1.7–4.8)	34	2.9 (1.8–4.5)	26	2.3 (1.4–3.8)	3	1.9 (0.6–6.1)		
Pancreas	213	39	1.7 (1.2–2.5)	63	1.6 (1.2–2.2)	78	2.1 (1.6–2.8)	14	2.6 (1.5–4.6)		
<b>Urinary tract</b>											
Bladder	411	122	3.2 (2.6–4.0)	284	4.2 (3.5–4.9)	288	4.4 (3.7–5.2)	42	4.6 (3.3–6.4)		
Renal pelvis	13	4	4.2 (1.3–13.5)	12	6.9 (2.9–16.3)	8	4.9 (1.9–12.9)	1	nd		
Ureter	8	3	4.7 (1.2–18.4)	13	10.5 (4.1–26.6)	7	5.6 (1.9–16.4)	0	nd		
Kidney	291	53	1.9 (1.4–2.6)	67	1.4 (1.0–1.8)	88	1.9 (1.4–2.4)	9	1.4 (0.7–2.7)		
<b>Other</b>											
AML	63	13	2.1 (1.1–3.9)	23	2.1 (1.3–3.6)	23	2.3 (1.4–3.9)	2	nd		

nd, not determined; AML, acute myeloid leukemia.

<sup>a</sup>Referent group: never smokers are participants who did not smoke cigarettes, pipes or cigars.

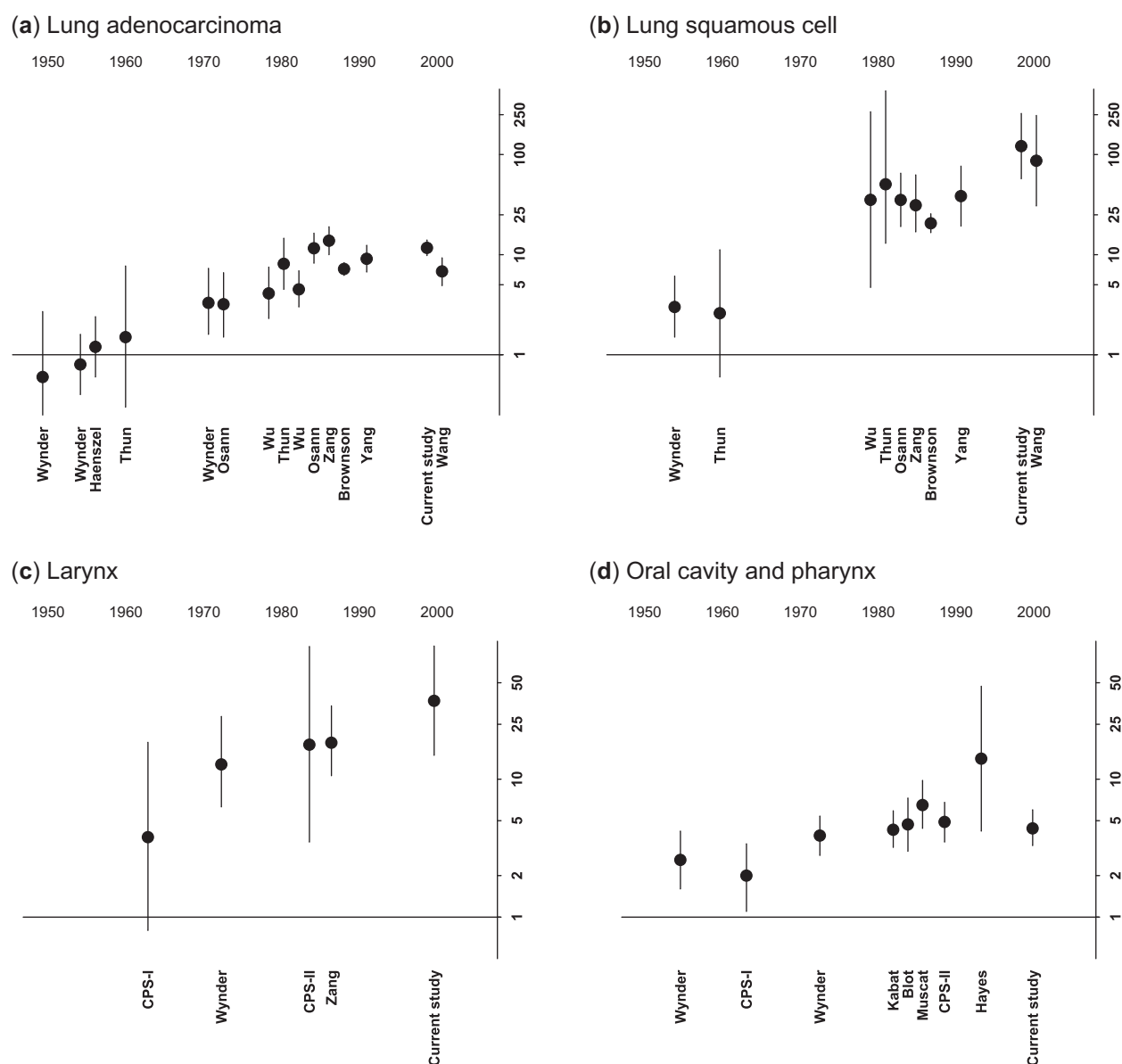
<sup>b</sup>Adjusted for age, education, alcohol intake, self-reported ethnicity and smoking pipes or cigars.

review, whereas RRs among women strengthened over time. In contrast, RRs for cigarette smoking and each major histological subtype of lung cancer appeared to increase in men over the course of the 20th century, as we also observed for women. Such findings likely do not reflect changes in cigarette use per day. Higher RRs for lung cancer in the more recent studies persisted within specific levels of cigarettes per day or pack-years. Also, smokers in our cohort tended to smoke fewer cigarettes per day than in earlier US studies, reflecting similar declines for cigarettes per day in the US population.<sup>5,16</sup> Concordant with our results, mortality rates for each of these histological subtypes were higher in male current smokers in the Cancer Prevention Study (CPS)-II, with follow-up from 1982 to 1984, than in CPS-I with follow-up from 1959 to 1961.<sup>8</sup> Supporting these findings, modelling studies have

also shown that the relative risks from CPS-I underestimated subsequent US lung cancer mortality rates, and in particular the rise of lung adenocarcinoma.<sup>2,17,18</sup>

Analogous findings in the USA have been reported for incident bladder cancer, in which associations with smoking were stronger in the current cohort<sup>19</sup> and the New England Bladder Cancer Study<sup>20</sup> than in previous studies. Associations between smoking and total mortality also strengthened in the USA and the UK over the 20th century in both women and men.<sup>6,7,21,22</sup>

Strengthening associations between cigarette smoking and some cancers may reflect widespread changes in the design and construction of cigarettes.<sup>2,8</sup> Such changes could have affected both smoking behaviour and the distribution of carcinogens present in tobacco smoke.<sup>9</sup> These changes might have differential effects across the spectrum



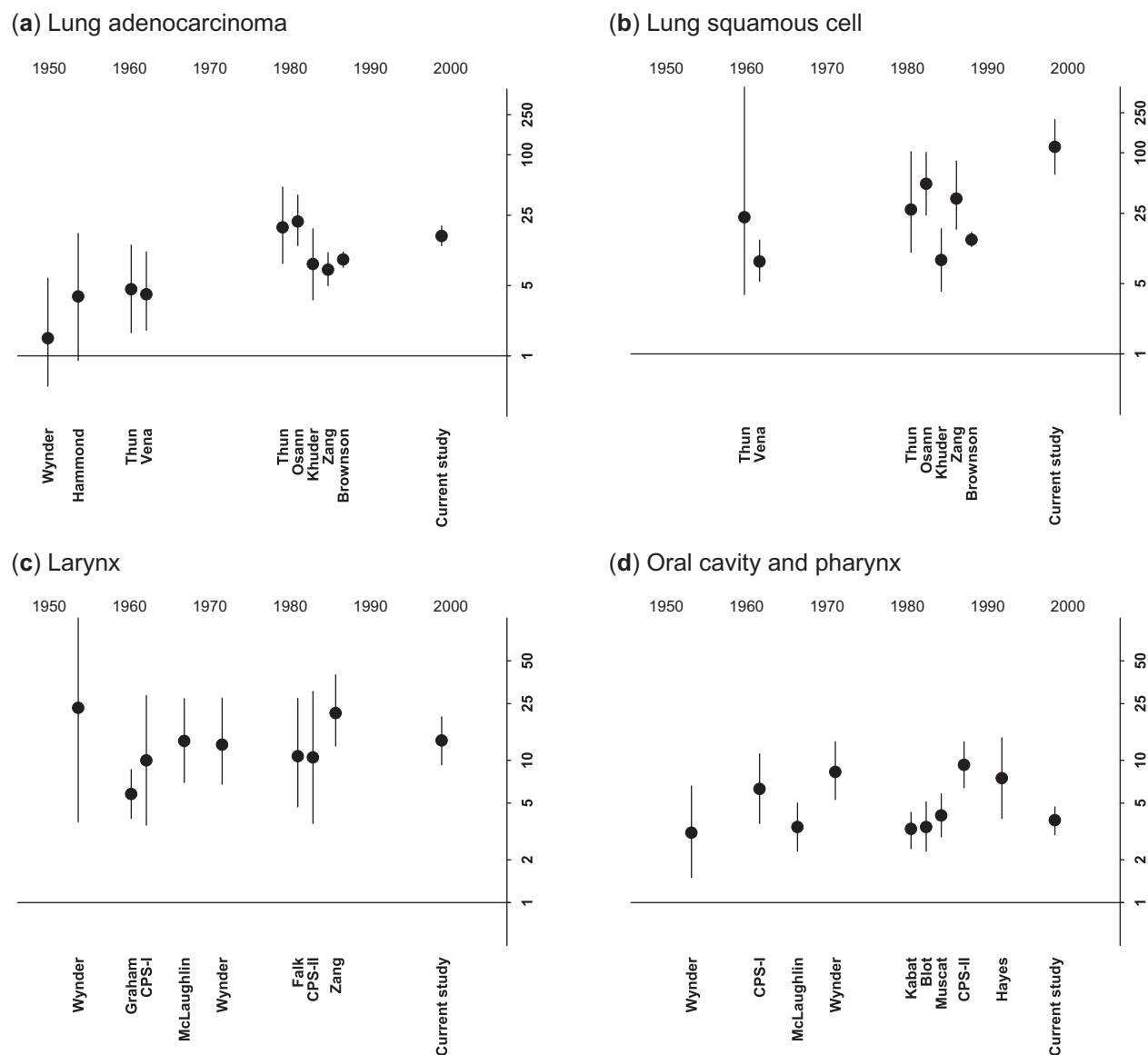
**Figure 2.** Current cigarette use and lung and head and neck cancer by study year, in women. Relative risks for current vs never smoking are plotted on the y-axis, using a log scale. Year is on the x-axis. Plotted circles represent the point estimate and whiskers reflect the 95% confidence intervals. Each study is plotted by the mid point of when it was conducted, and labelled with the first author of the associated publication. Horizontal line represents a relative risk of 1. (a) Lung adenocarcinoma; (b) lung squamous cell carcinoma; (c) larynx; (d) oral cavity and pharynx.

of tobacco-related cancers, suggesting an explanation for higher smoking-related risks of lung and bladder cancer in men yet constant risks of laryngeal, oral cavity and pharyngeal cancer. Recent data suggesting specific associations between certain tobacco-specific nitrosamines and particular forms of cancer<sup>23</sup> support this hypothesis.

As cancers of the head and neck are additionally caused by alcohol<sup>24</sup> and human papillomavirus (HPV),<sup>25</sup> it is also possible that historical changes in these or possibly other risk factors may have obscured the effects of changing cigarettes on these sites. As our study lacked biological samples, we were unable to test for HPV or other cancer risk

factors requiring biological samples such as *Helicobacter pylori*, hepatitis B and hepatitis C. Future studies that include biological samples are needed to examine associations of cigarette smoking and cancer in the context of these risk factors in contemporary birth cohorts of women and men.

Higher RRs of certain smoking-related cancers could also reflect decreasing incidence rates in never smokers, which would cause the RRs for smoking to increase even if absolute risks were unchanged. However, data from three consortial projects<sup>7,26,27</sup> indicate that the rates of lung cancer in never smokers remained constant, or possibly



**Figure 3.** Current cigarette use and lung and head and neck cancer by study year, in men. Relative risks for current vs never smoking are plotted on the y-axis, using a log scale. Year is on the x-axis. Plotted circles represent the point estimate and whiskers reflect the 95% confidence intervals. Each study is plotted by the mid point of when it was conducted, and labelled with the first author of the associated publication. Horizontal line represents a relative risk of 1. (a) lung adenocarcinoma; (b) lung squamous cell carcinoma; (c) larynx; (d) oral cavity and pharynx.

increased, over the last 50 years. Other factors, such as increases in fine particulate air pollution (PM<sub>2.5</sub>), may also have influenced lung cancer trends in never smokers, particularly trends in adenocarcinoma.<sup>28</sup>

Current smokers in the US population tend to have less education than never smokers and this was reflected in our cohort. Concerns have been raised that such differences could confound associations between smoking and cancer.<sup>29</sup> However, we observed strong associations between smoking and cancer across strata of educational status, suggesting socioeconomic differences between smokers and non-smokers had little effect on our relative risks.

Strengths of our study include prospective assessment of cigarette use and very large size, allowing examination of nasopharynx, ureter and other relatively uncommon cancers that are rarely investigated in prospective cohort studies. We examined incident cancers, important as cigarette smoking can affect both cancer development and survival,<sup>30</sup> and comparisons of incident cancer are less affected by historical changes in treatment than are studies of cancer mortality. Unlike most mortality studies, we were able to investigate associations between cigarette smoking and specific histological subtypes of oesophageal and lung cancer, observing associations of substantially different magnitude for each subtype. Inclusion of both

women and men allowed us to directly compare risks between them.

Limitations include a lack of information on smoking initiation for the full cohort and assessment of smoking at only a single time-point. During follow-up, some current smokers probably quit, which would attenuate observed associations for current smoking. However, as our RRs were only moderately higher in analyses restricted to the first 6 years of follow-up (data not shown), we present results for the entire follow-up period to maximize statistical power. Also, our results may not apply to other populations with different smoking prevalence and different cigarette composition. For example, recent data from the European Prospective Investigation into Cancer cohort revealed lower RRs in women than men for current smoking and different cancer types,<sup>31</sup> likely reflecting less lifetime smoking history in the women relative to the men of this cohort. However, our results do likely apply to the UK and other countries where women and men have similar smoking patterns.

In conclusion, our data indicate that falling age of smoking initiation in women and other historical changes in US cigarette smoking patterns have altered associations with incident cancer. With now similar lifelong smoking patterns, relative risks and population-attributable fractions for cigarette smoking and cancer in women are now broadly similar to those found in men. Cigarette smoking remains a critical determinant of cancer in the USA and elsewhere. Further reductions in cigarette smoking are urgently needed.

## Supplementary Data

Supplementary data are available at *IJE* online.

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